

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Withdrawn) A non-parenteral multi-particulate formulation comprising:

a plurality of carrier particles;

an oligonucleotide to be delivered across a mucosal membrane; and

a penetration enhancer selected from the group consisting of a fatty acid, bile salt, chelating agent and non-chelating non-surfactant,

wherein said fatty acid is selected from the group consisting of oleic acid, lauric acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprates, monoolein, dilaurin, caprylic acid, arachidonic acid, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, monoglycerides, diglycerides, and salts thereof.
2. (Withdrawn) The formulation of claim 1, wherein said oligonucleotide is an antisense oligonucleotide.
3. (Withdrawn) The formulation according to claim 2, wherein said oligonucleotide is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:7.
4. (Withdrawn) The formulation according to claim 1, wherein said carrier particles are bioadhesive.

5. (Withdrawn) The formulation according to claim 1, wherein said carrier particles comprise a particle-forming substance selected from the group consisting of poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pullulans, celluloses and starches.

6. (Withdrawn) The formulation according to claim 1, wherein said carrier particles comprise a particle-forming material selected from the group consisting of chitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylamino-methylethylene P(TDAE), polyaminostyrene (e.g. p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcyanoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), and polyethyleneglycol (PEG).

7. (Withdrawn) The formulation according to claim 1, wherein said carrier particles are polycationic.

8. (Withdrawn) The formulation according to claim 1 wherein said carrier particles comprise a complex of poly-L-lysine and alginate; or protamine and alginate, lysine, dilysine, trilysine, calcium, albumin, glucosamine, arginine, galactosamine, nicotinamide, creatine, lysine-ethyl ester and arginine-ethyl ester.

9. (Withdrawn) The formulation according to claim 1, wherein said carrier particles are other than polycationic.

10. (Withdrawn) The formulation according to claim 9, wherein said carrier particles comprise poly(DL-lactic co-glycolic acid) (PLGA).

11. (Withdrawn) The formulation according to claim 1, wherein said carrier particles are miniparticles.

12. (Withdrawn) The formulation according to claim 1, wherein said carrier particles are microparticles.

13. (Withdrawn) The formulation according to claim 1, wherein said carrier particles are nanoparticles.

14. (Withdrawn) The formulation according to claim 1, wherein said penetration enhancer is selected from the group consisting of fatty acids, bile acids and salts and mixtures thereof.

15. (Withdrawn) The formulation according to claim 1, wherein said penetration enhancer is selected from UDC, CDCA and salts and mixtures thereof.

16. (Withdrawn) The formulation according to claim 1, wherein said penetration enhancer is a mixture comprising the sodium salts of UDCA, capric acid and lauric acid.

17. (Withdrawn) The formulation according to claim 1 wherein said penetration enhancer is a component of said particle.

18. (Withdrawn) The formulation according to claim 1, wherein the surface of said carrier particle is substantially coated with said penetration enhancer.

19. (Withdrawn) The formation according to claim 1, further comprising a mucolytic material.

20. (Withdrawn) The formulation according to claim 19, wherein said mucolytic material is selected from the group consisting of N-acetylcysteine, dithiothreitol, pepsid, pilocarpine, guaifenesin, glyceryl guaiacolate, terpin hydrate, ammonium chloride, guattenesin, ambroxol, bromhexine, carbocysteine, domiodol, letosteine, mecysteine, mesna, sobrerol, stepronin, tiopronin and tyloxapol.

21. (Withdrawn) The formulation to claim 1 in a dosage form selected from the group consisting of tablets, capsules and filled gelcaps.

22. (Withdrawn) The formulation according to claim 21, further comprising an

enteric material protecting the dosage form from degradation in a gastric environment.

23. (Withdrawn) The formulation according to claim 22, wherein said enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), propylene glycol, EUDRAGIT and sorbitan monoleate.

24. (Withdrawn) The formulation according to claim 22, wherein said enteric material substantially coats the outer surface of the dosage form.

25. (Withdrawn) The formulation according to claim 22, wherein said enteric material substantially coats the outer surface of the individual carrier particles.

26. (Currently Amended) A method of delivering a biologically active substance across a mucosal membrane, comprising introducing to the mucosal membrane a non-parenteral multi-particulate formulation ~~according to claim 1~~ comprising:

a plurality of carrier particles;

an oligonucleotide to be delivered across a mucosal membrane; and

a penetration enhancer selected from the group consisting of a fatty acid, bile salt, chelating agent and non-chelating non-surfactant,

wherein said fatty acid is selected from the group consisting of oleic acid, lauric acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprinate, tricaprinate, moolein, dilaurin, caprylic acid, arachidonic acid, glyceryl 1-monocaprinate, 1-

dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, monoglycerides, diglycerides, and salts thereof.

27. (Original) The method according to claim 26, wherein said biologically active substance is an oligonucleotide and said formulation is administered orally to a mammal.

28. (Withdrawn) A non-parenteral multi-particulate formulation comprising:
a plurality of carrier particles;
an oligonucleotide to be delivered across a mucosal membrane; and
a penetration enhancer selected from the group consisting of a fatty acid, bile salt, chelating agent and non-chelating non-surfactant.